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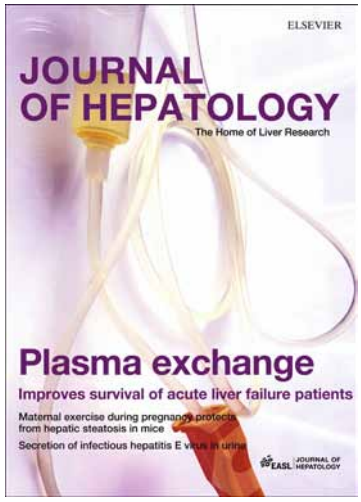

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GUT – LIVER IMMUNITY

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Summary

The liver contributes to immune surveillance against pathogens entering via the gut and is itself influenced by alterations in mucosal immune responses and the microbiome. Mucosal immunity is also implicated in autoimmune liver diseases that associate with inflammatory bowel disease (IBD), and in steatohepatitis where compromised enteric barrier function and altered bacterial sensing drive liver inflammation. In this article, we discuss recent advances in our understandings of how dysregulated mucosal immune responses result in hepatobiliary injury; specifically through defective intestinal barrier function, changes in the enteric microbiome and loss of immune tolerance, and via shared leucocyte recruitment pathways.

Dysregulated epithelial integrity and enteric dysbiosis

The intestinal and biliary epithelia are continuous, sharing many properties including expression of tight junction proteins such as E-Cadherin, pattern recognition receptors (PRR), and an ability to release secretory IgA. The intestinal epithelial barrier does not, however, completely impede luminal antigens from entering tissues, although penetration beyond the gut is typically restricted by local immunity. In particular, the sub-epithelial lamina propria (LP) contains numerous antigen-presenting dendritic cells (DC) that sample and process commensal and pathogenic bacteria from within the lumen. DC subsequently migrate to draining mesenteric lymph nodes (MLNs) or Peyer's patches in order to prime naïve T-cells with gut-tropism. Ordinarily, enteric commensals and pathogens are confined to the gut by MLN; however, in the presence of intestinal inflammation and increased permeability, live enteric bacteria can be detected in the liver where they are contained by the local action of Kupffer cells. Thus, the liver functions as second “firewall” that clears commensals from the circulation if intestinal defences are overwhelmed [1]. In the presence of liver

dysfunction this second firewall fails, leading to bacteria in the systemic circulation and sepsis associated with liver failure. Furthermore, onset of portal hypertension may result in congestion and oedema of the intestine, thereby enhancing passage of microbes beyond the gut lumen, contributing to spontaneous peritonitis and bacteraemia.

Intestinal $CX_3CR_1^+$ macrophages are another critical component of the intestinal barrier. These cells use toll-like receptors (TLR) to sense micro-organisms and activate innate lymphoid cells to secrete IL-22, which directly promotes epithelial integrity and repair [2]. Deletion of CX_3CR_1 not only results in increased bacterial translocation and susceptibility to colitis, but in a diet-induced model of fatty liver disease to steatohepatitis, demonstrating how defects in gut integrity can drive hepatic inflammation [3].

Kupffer cells, hepatic sinusoidal endothelial cells (HSEC) and cholangiocytes all express PRR allowing them to respond to gut-derived bacterial products, although Kupffer cells are relatively resistant to endotoxin, preventing their perpetual activation under normal conditions. However, genetic polymorphisms that reduce the threshold for PRR-signalling may allow liver inflammation to occur in response to commensal flora; whereas others, for instance fucosyltransferase variants in primary sclerosing cholangitis (PSC), result in a divergent microbiome, generation of toxic bile acids and liver injury [4]. Dietary changes and gut inflammation can also result in enteric dysbiosis. For example, high fat diets skew the phyla ratio between *Firmicutes* and *Proteobacteria* to *Bacteriodes* resulting in activation of the inflammasome and generation of steatohepatitis in mice [5].

Immune activation and impaired tolerance in autoimmune liver disease

To maintain immune homeostasis, mucosal and hepatic immune responses to commensal bacteria and harmless food antigens need to be suppressed. Regulatory T-cells (T_{reg}) are critical for this, and mice that have defective T_{reg} as a consequence of deletion of the IL-2 receptor develop spontaneous colitis and cholangitis. This is of direct clinical relevance because in PSC, IL-2 receptor polymorphisms associate with reduced numbers of functional T_{reg} [6].

Enteric dysbiosis can result in exacerbated pro-inflammatory immune responses, wherein microbiota-induced T_{reg} expressing the nuclear hormone receptor RORγt actively differentiate into T_h17 cells [7]. Notably, autoimmune liver diseases are characterised by heightened T_h17 responses to pathogens, and polymorphisms in *CARD9* and *REL,* both of which are implicated in T_h17 differentiation, are associated with PSC [4]. IL-17-producing cells are abundant in the liver and intestine. In the gut, they are maintained by commensal bacteria which induce innate lymphoid cells to secrete IL-22 that in turn stimulates epithelial secretion of serum amyloid A; a critical factor for IL-17A expression in T-cells [8]. In both compartments IL-17-secreting T-cells express the lectin receptor CD161 [9], and use CCR6 to respond to CCL20 expressed by intestinal and biliary epithelium [10]. Primary biliary cirrhosis is associated with genetic variants of CCL20 providing further evidence for the role of mucosal immunity in immune-mediated bile duct damage [11].

Mucosal lymphocyte recruitment in PSC

Mucosal lymphocytes are characterised by the expression of molecules associated with gut tropism, specifically the integrin α4β7 and chemokine receptor CCR9, that become imprinted by intestinal DC in a process dependent on retinoic acid [4]. Mucosal lymphocytes are compartmentalised to the gut by their ability to respond to gut-selective endothelial adhesion molecules and chemokines; the most important of which are mucosal addressin cell-adhesion molecule-1 (MAdCAM-1) and CCL25. Normally these molecules are absent from the liver but under certain inflammatory conditions they are detected on hepatic endothelium promoting the aberrant recruitment of gut-derived $\alpha4\beta7^{+}CCR9^{+}$ effector lymphocytes. These effector cells can then exploit CCR6 to localise to biliary epithelium, where they drive liver injury [4].

Hepatic expression of MAdCAM-1 is partially regulated through vascular adhesion protein (VAP)-1, an ectoenzyme and endothelial adhesion molecule expressed in the liver. VAP-1 deaminates primary amines, perhaps those generated in the gut by bacteria dominating the microbiome in PSC, producing catabolites that drive NF*k*B-dependent endothelial expression of MAdCAM-1 required for the recruitment of mucosal lymphocytes [4]. Thus, we can propose a model that brings together defective gut barrier function, nutrients, dysbiosis and aberrant lymphocyte homing to explain the link between IBD and liver disease (**Figure 1**). This model has therapeutic implications because if correct, drugs targeting CCR9, MAdCAM-1 or α4β7 for the treatment of Crohn's disease and ulcerative colitis could also be effective for IBD-associated liver diseases.

Figure 1: Gut-Liver Immunity in Primary Sclerosing Cholangitis (PSC)

[**Top Panel**] In a genetically predisposed individual, alterations in the gut microbiome [A], or abnormal handling of commensal species through epithelial pattern recognition receptor (PRR) defects [B] may result in heightened innate immune activation as well as toxic bile acid transformations [C]. Naïve lymphocytes, imprinted with gut-tropism by intestinal dendritic cells (DC) [D], localise within the intestinal mucosa via MAdCAM-1/$\alpha 4\beta 7$ and CCL25/CCR9 dependent mechanisms. Effector (as opposed to regulatory) T-cell responses predominate in IBD [E] driving intestinal inflammation leading to a defective epithelial barrier [F], exacerbated by the loss of protective macrophage populations [G].

[**Middle Panel**] As a consequence of intestinal inflammation enteric pathogens translocate beyond the mucosal barrier to the portal circulation and liver where they can drive local inflammation via PPR activation [H]. Mucosal effector lymphocytes bearing a 'gut-tropic' phenotype are recruited in response to hepatic endothelial expression of CCL25 and MAdCAM-1 [I] together with effector cells primed locally [J]. The adhesion molecule and ectoenzyme VAP-1 is upregulated during chronic inflammation and supports both lymphocyte adhesion directly [K] and catabolises amine substrates secreted by gut bacteria resulting in upregulation of several endothelial adhesion molecules, including MAdCAM-1, on sinusoidal endothelium [L]. Recruited effector cells overwhelm local regulatory networks (M).

[Bottom Panel] After entering the liver, effector cells use chemokine receptors such as CCR6 to respond to chemokines secreted by epithelial target cells (hepatocytes [N] or biliary epithelium [O]) resulting in cell-mediated immunological attack and bile duct destruction. Hepatobiliary damage is likely to be enhanced through the action of toxic bile acids and heightened PRR activation.

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